

Backup Slides Shown

HPV Positivity in Cervical Cancers

Detected Using Liquid Cytology or Separate Swab

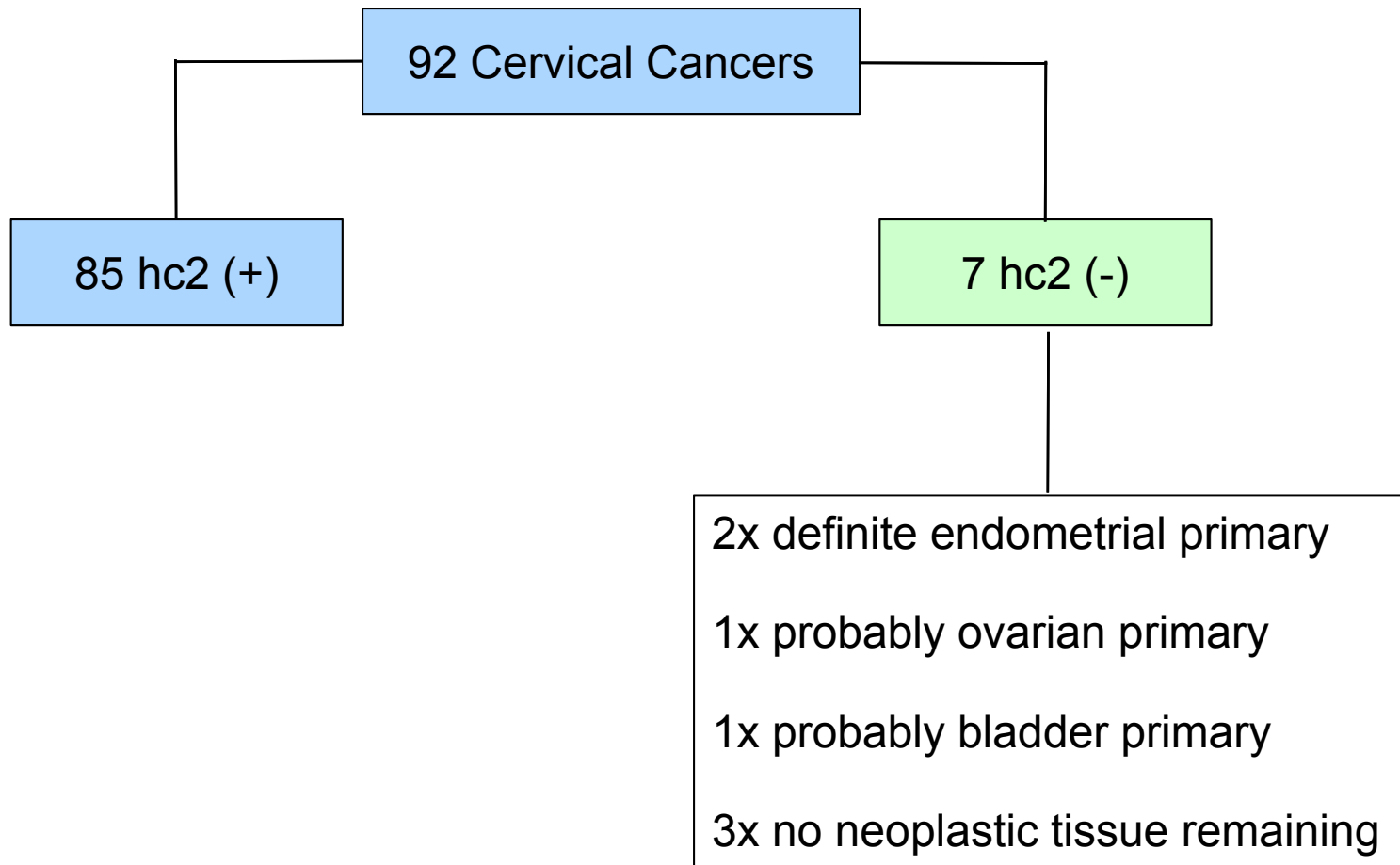
	Number of Cancers	Method	% HPV Pos
Kang (Korea) ¹	198	hc2	93%
Wu (China) ²	475	hc2	90%
Bohmer (Germany) ³	92	hc2	92%
Wang (China) ⁴	30	PCR	100%
ATHENA	8	cobas	100%
UNM	18	cobas	94%
Cape Town	50	cobas	94%

¹ Kang et al. IJGC 2009;19:924; ² Wu et al. JCV 2006;35:264; ³ Bohmer et al. AJOG 2003;189:118;

⁴ Wang et al. APJCP 2013;14:92979.

HPV Positivity in Cervical Cancers

Detected Using Separate Swab and hc2



Impact of Vaccination Against HPV

- No question that once there is widespread vaccination there will be an impact on:
 - HPV prevalence (esp. 16/18 but also others)
 - Prevalence of cytologic abnormalities
 - Prevalence of CIN2+ lesions
- Magnitude of effect depends on vaccination coverage, number of doses and age of vaccination
- Reduction in \geq CIN2 will reduce the PPV of both cytology and HPV testing, **but cytology is more subjective and will be impacted more**

Sensitivity of cobas[®] HPV Test vs. Cytology to Detect Invasive Cancer

	cobas [®] HPV Test+	Cytology+
ATHENA n=8	8	7
UNMHPVP Registry n=18 ²	17¹	16
Total	25	23

- Sensitivity of cobas[®] HPV Test: $25/26 = 96.2\%$
- Sensitivity of Cytology: $23/25 = 92\%$

¹ 1 case determined to be a poorly differentiated adenocarcinoma with origin uncertain, endocervical vs. endometrial; ² 1 case of endometrial cancer was found to have been sent in error after HPV testing was performed at RMS and 1 case was determined to be cobas[®]HPV “invalid” due to clotting of sample; these cases were excluded from the analysis

Sensitivity of cobas HPV Test to Detect Invasive Cancer: University of Cape Town Study

Study Design: 50 successive samples were collected in PreservCyt medium from eligible women presenting for treatment at University of Cape Town following diagnosis of invasive cervical cancer. Biopsy histology was reviewed and confirmed by consensus of expert pathologists. Testing with the cobas HPV Test was performed at RMS

cobas HPV Test+	47
cobas HPV Test–	3^{1,2}
Total	50

¹ 1 negative case determined to be HPV 82+

² 2 negative cases were documented to have been sampled from large visible fungating lesions.

Sensitivity of cobas HPV Test = 94%

Summary of Demographic Characteristics of Screening Women Who Were Selected for Follow-up

Characteristics	Statistic	Evaluable Subjects N=7,636
Age (Years)	Mean	39.3
	SD	11
	Median	38
	(Min, Max)	(25, 93)
Age Group (Years)		
25-29	n (%)	1,801 (23.6)
30-39	n (%)	2,459 (32.2)
40-49	n (%)	1,932 (25.3)
≥50	n (%)	1,444 (18.9)
Race		
White	n (%)	6,061 (79.4)
American Indian or Alaskan Native	n (%)	46 (0.6)
Black or African American	n (%)	1,347 (17.6)
Asian	n (%)	123 (1.6)
Native Hawaiian or Other Pacific Islander	n (%)	13 (0.2)
Any Combination¹	n (%)	46 (0.6)
Ethnicity		
Hispanic or Latino	n (%)	1,493 (19.6)
Not Hispanic or Latino	n (%)	6,143 (80.4)

¹Any Combination refers to subjects who selected more than one race.

Candidate Performance in Detecting \geq CIN3 in Hispanic Women ATHENA (\geq 25 Years)¹

	Hispanic
Relative Sensitivity ²	1.30
Relative Specificity ²	1.03
PPV (%)	13.99
NPV (%)	99.75
PLR	17.31
NLR	0.27

¹Data not reviewed by FDA

²Relative to comparator (cytology alone)

Performance Comparison

25-29 Years vs. ≥30 Years

Age Group	Statistic	Candidate	Comparator
25-29	Relative sensitivity	1.66*	1.00
	Relative specificity	1.00	1.00
≥30	Relative sensitivity	1.26*	1.00
	Relative specificity	1.02*	1.00

*VBA differences statistically significant
Data not submitted for FDA review

Candidate Demonstrates Significantly Improved Predictive Values Compared to Cytology 25-29 Years

Description	≥CIN2			
	PPV ¹ (%)	NPV ¹ (%)	PLR ¹ (%)	NLR ¹ (%)
Comparator	13.40	98.43	5.52	0.57
Candidate	17.88	99.07	7.77	0.34
Difference	4.48* (2.19, 6.65)	0.64* (0.35, 0.88)	2.25* (1.11, 3.36)	-0.23* (-0.32,-0.13)

*Statistically significant difference

XX-17

Measures of Clinical Resources Utilization for Disease (\geq CIN3) in 25-29 Years (VBA)

Algorithm	Description	Number of Screening Tests	Number of Screening Tests Per CIN3+	Number of Colposcopies	Number of Colposcopies Per CIN3+	Number of CIN3+ Cases Missed
Comparator	Cytology Alone	6654	150.6	652	14.8	58
ASC-US triage	ASC-US Triage 25+	6994	158.3	480	10.9	58
Candidate	HPV with 16/18 Genotyping	7596	103.6	704	9.6	29
ATRI NM \geq 30	ASC-US Triage 25-29 and ASC-US Triage NILM 16+/18+ 30+	6994	158.3	480	10.9	58

Comparison of Performance Candidate vs. Comparator to Detect \geq CIN3 in Women \geq 25 Years, Directed and Random Biopsy

Description	\geq CIN3	
	Relative Sensitivity ¹ %	Relative Specificity ¹ %
Directed only:		
Comparator	1.00	1.00
Candidate	1.41*	1.02*
Directed and Random Combined		
Comparator	1.00	1.00
Candidate	1.37*	1.02*

Using only data from the Directed biopsy (ie excluding the Random biopsy) shows the same superior performance of the Candidate algorithm over the Comparator

¹Relative to Cytology alone

*Statistically significant difference between Candidate and Comparator

Data not reviewed by FDA

Comparison of Performance Candidate vs. Comparator to Detect \geq CIN3 in Women \geq 25 Years, Directed and Random Biopsy

Description	\geq CIN3			
	PPV %	NPV %	PLR	NLR
Directed only:				
Comparator	4.70	99.58	7.08	0.60
Candidate	9.16*	99.72*	14.46*	0.41*
Directed and Random Combined				
Comparator	6.47	99.41	7.06	0.61
Candidate	12.25*	99.58*	14.24*	0.44*

Using only data from the Directed biopsy (ie excluding the Random biopsy) shows the same superior performance of the Candidate algorithm over the Comparator

*Statistically significant difference between Candidate and Comparator
Data not reviewed by FDA

cobas[®] HPV Test Results and Pap Category in 12 hrHPV+ by Age Group

	25-29 Years n (%)	≥30 Years n (%)
HPV 16/18+	464 (7.0)	706 (2.1)
12 other hrHPV ≥ASC-US	240 (3.6)	480 (1.4)
12 other hrHPV NILM	702 (10.6)	1,691 (4.9)
HPV-	5,248 (78.6)	31,413 (91.6)
Total	6,654	34,290

HPV Negative CIN2+ Cases in the ASC-US Population in ATHENA

- 77 cases CIN2+ in women ≥ 21 years with ASC-US
- 8 cases were hrHPV-
- 3 occurred in ≤ 40 years
 - 1 was HPV82+ and was p16+
 - The other 2 were p16-
- 5 cases occurred in women > 40 years
 - 3 were p16-

Performance Summary of Candidate and Comparator Algorithms in Detecting \geq CIN3 (Adjusted) in Vaccinated Women

Algorithms	Sensitivity	Specificity	100-Specificity	PPV	NPV	PLR	NLR
Candidate	66.7%	89.8%	10.2%	7.5%	99.5%	6.54	0.37
Comparator	50.0%	88.4%	11.6%	5.1%	99.3%	4.29	0.57